Watts et al. (Lancet 1992, 339:563-569; hereafter "Watts"), and Demopulos et al. (U.S. Patent No. 5,800,385; hereafter "Demopulos").

Rejections under 35 U.S.C. 112, first paragraph

Claims 55-60, 62, 63, 65-68, 70, and 71 stand rejected for lack of enablement on the basis that "[g]iven that ... no common core structural, physical or chemical properties of the cholesterol synthesis inhibitors or cholesterol transfer inhibitors have been provided, the skilled artisan would be required to conduct undue experimentation in order to select compounds that will be useful in the practice of the instant invention." Applicants respectfully disagree.

The skilled artisan in the instant case is a physician experienced with treating patients with heart disease. For the purposes of the instant invention, it is not necessary for the physician to understand the precise mechanism of action of a cholesterol synthesis or transfer inhibitor. Rather, the physician merely needs to employ a compound that lowers the cholesterol level of the patient; whether that occurs by inhibition of cholesterol synthesis or transfer is unimportant. Moreover, there is no reason to believe that any given compound that lowers cholesterol levels (whether by inhibition of cholesterol synthesis or transfer) would not be beneficial in the claimed methods. Accordingly, common core structural, physical, or chemical properties of the cholesterol lowering drugs are not necessary. Applicants further point out that, in general, physicians do not develop new drugs; they administer those already on the market. No experimentation is

thus required in order to select a cholesterol synthesis or transfer inhibitor because a physician employing the instant methods needs only to administer one of the many available drugs that inhibits cholesterol synthesis or transfer. Knowing the desired effect of a cholesterol synthesis or transfer inhibitor is the only information a physician needs in order to practice the present invention, and the rejection of claims 55-60, 62, 63, 65-68, 70, and 71 for lack of enablement may therefore be withdrawn.

Rejections under 35 U.S.C. 112, second paragraph

Claims 55-71 also stand rejected for indefiniteness for reciting "cholesterol transfer inhibitor." The term "cholesterol transfer inhibitor" is defined as "any compound which retards or blocks the formation of cholesterol ... esters from non-cholesterol sources.... [T]he inhibitor ... may ... act by retarding the action of acetylcholesterol acyl transferase." (pg. 7, ll. 3-7) Thus, a cholesterol transfer inhibitor is any compound that prevents the formation of a cholesterol ester, typically by inhibiting a transferase enzyme. As with cholesterol synthesis inhibitors, the prior art contains numerous examples of cholesterol transferase inhibitors. Applicants submit abstracts from Chiari et al. (Pharmacol. Res. 1996, 33:181-189) and Nicholson et al. (Lipids 1995, 30:771-774) as evidence that these compounds are known in the art.

In addition, the Office is directed to M.P.E.P. § 2173.01, which states:

> [A]pplicants are their own lexicographers. They can define in the claims what they regard as their invention essentially in whatever terms they choose so long as the terms are not used in ways that are contrary to accepted meanings in the art. Applicants may use functional language ...

which makes clear the boundaries of the subject matter for which protection is sought.

In the instant claims, the term "cholesterol transfer inhibitor" is defined in the specification based on its function as an inhibitor of cholesterol esterification. As stated above, one skilled in the art is a physician who, based on the terminology used in the claims and the description in the specification of the desired outcome, can select an appropriate cholesterol transfer inhibitor from those available. Based on the foregoing arguments, the indefiniteness rejection should be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 55-71 stand further rejected for obviousness over Sassen, Vane, Lee, Watts, and Demopulos. Applicants respectfully traverse this rejection.

Claim 55, from which all other claims depend, recites:

> 55. A method for reducing coronary artery stenosis by at least 20% in a mammal comprising the administration to said mammal of a combination of (a) a composition comprising eicosapentaeneoic acid or docosahexaeneoic acid and (b) a cholesterol synthesis or transfer inhibitor, in combination with limiting fat or cholesterol intake, whereby a serum LDL concentration of less than or equal to 70 mg/dl is achieved. (emphasis added)

The present claims are thus all directed to methods for reducing narrowing in coronary arteries using a combination therapy requiring three components: (1) eicosapentaeneoic acid or docosahexaeneoic acid, (2) a cholesterol synthesis or transfer inhibitor, and (3) limiting fat or cholesterol intake.

M.P.E.P. § 2142 states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant□s disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991).

This standard has not been met in this case. Applicants assert that the prior art provides neither the suggestion nor the motivation to combine the cited references, nor does the combination of the cited references teach or suggest all of the limitations of the claimed invention. Moreover, the cited references provide no reasonable expectation that such a combination would have led to success.

The references do not teach or suggest all of the claim limitations.

The instant claims are directed to methods of reducing coronary artery stenosis by 20% by treatment with eicosapentaeneoic acid or docosahexaeneoic acid, a cholesterol synthesis or transfer inhibitor, and limited fat or cholesterol intake. The instant methods are for a reduction in stenosis, i.e., the widening of coronary arteries already occluded, which is distinct from a prevention of stenosis, for example after angioplasty, i.e., restenosis.

The Office has cited Sassen, Lee, Vane, and Watts as teaching the three major components of the claimed methods, with Demopulos cited as teaching an additional

element in claim 70. While the cited art does disclose some of the individual elements of the claimed methods, they do not suggest the desirability of the unique combination of the claimed method. Sassen reviews several studies on the use of fish oil for the prevention and regression of atherosclerosis. Vane discloses the use of aspirin and fish oil for the prevention of thrombosis. Lee discloses the use of pravastatin, niacin, and LDL apheresis for the prevention of restenosis after angioplasty. Watts teaches the use of a controlled diet, with or without administration of cholestyramine, for the regression of atherosclerosis. Demopulos teaches the use of a solution of various compounds, potentially including buspirone, to inhibit undesirable effects (e.g., pain, inflammation, spasm, and restenosis) of cardiovascular therapeutic and diagnostic procedures.

Applicants maintain their position that nothing in these references pinpoints even two of the three major components of the claimed methods, nor do these references provide a basis for choosing such elements from the therapeutic suggestions listed. In addition, while Lee discloses the use of a cholesterol synthesis or transfer inhibitor, pravastatin, in a treatment for the prevention of restenosis after angioplasty, Lee fails to disclose that pravastatin is useful for the reduction of stenosis in patients already having occluded coronary arteries. Since the Office has failed to provide a combination of references that teach or suggest the use of all three of the major components in a method for reducing stenosis, the rejection should be withdrawn.

Furthermore, the instant claims are directed to a method for reducing coronary artery stenosis by at least 20%, and the prior art does not suggest such a reduction using

the instantly claimed methods. In response to this argument, the Office stated that "the percentage reduction of restenosis is exceeding 20% when treating with fish oil alone (See Sassen et al.)." As an initial note, a percentage reduction of restenosis (i.e., the recurrence of coronary narrowing after a widening procedure) is irrelevant to the instant claims, which are directed to methods of reducing stenosis (i.e., the narrowing already present in a coronary artery). In addition, the Office's statement is incorrect. Sassen provides no data showing a 20% reduction of stenosis. The statement therefore appears to relate to studies on the prevention of stenosis in autografted dogs (pg. 185).

In these studies, dogs were subjected to venous autografting and hypercholesteremia. The dogs were then fed fish oil in order to determine its effects on the rate of intimal proliferation. The 54% decrease in the acceleration of intimal proliferation relied upon by the Office is not equivalent to a 20% reduction in stenosis. In addition, one examining the data from two studies on dogs provided by Sassen would conclude that stenosis still increases with the use of fish oil. For example, in one study, the dogs with autografts had an intimal thickness of 23-24 μm after 6 weeks (compared to a 39 μm control thickness), and in a second study, dogs with autografts had intimal thicknesses of 57.5 μm and 77.2 μm after 3 months (compared to a 125 μm control thickness and a 143 μm control thickness, respectively). Thus, based on these data, one skilled in the art would conclude that fish oil, while perhaps slowing the increase of stenosis, does not prevent its progression or facilitate reduction. Accordingly, the data relied upon by the Office in fact teach away from the claimed method and are at best

irrelevant to the patentability of the instant claims, since the data relate to the rate of progression, and not reduction of stenosis. Since none of the references cited teaches or suggests a reduction of stenosis by at least 20% using the method of claim 55, the rejection for obviousness should be withdrawn.

There is no motivation to combine the references.

In addition to the deficiencies in the cited references, nothing in these references indicates that it would have been obvious to combine the therapeutic agents and behavioral modifications taught by the cited art. Indeed, the only basis for the combination of the cited art currently made of record is the assertion in the Office Action that "it flows logically to combine or incorporate agents, which are known to be useful individually for treating or preventing restenosis, into a single combination or method useful for the same purpose."

Assuming arguendo that the motivation asserted by the Office is proper (which Applicants do not concede), the cited references still fail to provide such motivation. At best, Lee teaches the use of a cholesterol synthesis or transfer inhibitor as <u>one</u> component of a treatment for the prevention of restenosis, but Watts and Vane are silent with regard to restenosis. Watts is directed to regression of atherosclerosis using diet and cholestyramine, and Vane is directed to anti-thrombotic therapy using fish oil and aspirin and does not discuss coronary narrowing in any context. In addition, while Sassen discusses preventing restenosis using fish oil, it also states that there is no conclusive

evidence that fish oil is effective (pg. 187-188). Based on this discussion, there is no motivation to combine either reference that discusses fish oil or the reference that discusses diet. Thus, there is no motivation of record to combine the references that purport to teach even two of the three major components of the instant claims.

Furthermore, there is no motivation to combine the methods of Watts with other cholesterol lowering drugs, as required by claim 55. While Watts teaches a diet-induced 23.3% reduction in stenosis (Table V, pg. 566), this level of reduction was found in only a small number of cases, and the result is thus not representative of the overall efficacy of the method. In addition, in similar cases where the patient received controlled diet and a cholesterol lowering drug, the reduction in stenosis was lower than that of diet alone. Thus, one reading Watts would not be motivated to combine diet with cholesterol lowering drugs to reduce stenosis by 20% because Watts observed reduced efficacy with such a combination.

As further support for this rejection, the Office also states:

> Agents causing vasodilatation and [preventing] platelet aggregation would have been reasonably expected to be useful in regression of atherosclerosis due to the role of platelet aggregation in atherogenesis. Moreover, aspirin would dilate the blood vessels, which is considered a direct counter effect of restenosis (narrowing).

The basis of this assertion, however, is unclear since Vane, which discusses vasodilatation and preventing platelet aggregation, nowhere teaches or suggests that such effects would be useful in a method of reducing stenosis. If the Office maintains this view, evidence supporting this assertion is required (M.P.E.P. § 2144.03).

There is no reasonable expectation of success.

In addition to the above, the obviousness rejection should also be withdrawn on a third basis – no reasonable expectation of success. The case law is clear that, for an invention to be obvious, there must be a reasonable expectation of its success. The instant claims are directed to methods for reducing coronary artery stenosis by at least 20%, and none of the cited references suggest that such a reduction is possible using the instantly claimed method.

As stated above, while Watts teaches 23.3% reduction in stenosis in limited cases using diet alone, the reduction in similar cases using diet and a cholesterol lowering drug was less than that of diet alone. Thus, Watts provides no reasonable expectation for a 20% reduction in stenosis in a method including both a controlled diet and cholesterol lowering drugs, as instantly claimed.

In addition, the Office states that "several studies [reviewed in Sassen] have shown that fish oil is effective in regression of human lesions." This statement is contradicted by the last sentence of Sassen, which states that "no attempts have been made to study the influence of n-3 fatty acids in the regression of human atherosclerosis." (pg. 188) In addition, the Office's reliance on Sassen's statements that "relatively advanced lesions can reduce in size over time" (pg. 186) is misplaced since those studies are based on treatment methods that do not include fish oil (a copy of Daoud et al. Arch. Pathol. Lab. Med. 1976, 100:372-379

referenced by Sassen is enclosed for the Examiner's review). Furthermore, Sassen states that, of the four studies on regression of atherosclerosis by treatment with fish oil, a study in pigs and a study in rabbits showed regression, a study in pigs showed no change, and a study in monkeys (the animal model closest to humans) showed atherosclerotic progression (pg. 187). Moreover, Sassen states that "the number of animal studies investigating the effects of fish oil on the regression of atherosclerosis is too small to draw any conclusion..." (pg. 188) Sassen therefore fails to provide any reasonable expectation that a treatment for reducing stenosis that included fish oil would be effective at all, much less induce a reduction by 20%, as required by claim 55.

In sum, Applicants submit that nowhere in the cited references is a *prima facie* case of obviousness for the methods of these claims established. The references, while providing a list of therapeutics and behavioral modifications, do not teach the unique combinations of claims 55-71, nor do they provide a motivation to combine the references or a reasonable expectation of their success. The § 103 rejection should be withdrawn.

Change of Address

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CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a petition to extend the period for reply for one month, to and including March 5, 2003. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 5 March 2003

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